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Original Research Article

Role of red blood cell distribution width to predict pulmonary hypertension secondary to chronic obstructive pulmonary disease

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Abstract

Introduction: Chronic Obstructive Pulmonary Disease (COPD) is a common, preventable and treatable disease, that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to gases or noxious particles. Over the past decade, RDW has been associated with incipient myocardial infarction and heart failure in the general population has emerged as the one of the strongest predictor of poor survival in patients with established heart failure and coronary artery disease.[12] RDW has also been proposed as marker of immune activation correlating with levels of tumour necrosis factor alpha and interleukin-6.The process of inflammation and dysregulated hematopoiesis may be linked, since interleukin6 is important for production of hepcidin in liver and thus may indirectly regulate iron metabolism.[13,14] Hence this study was conducted to observe Red Blood Cell Distribution Width in Patients with chronic obstructive pulmonary disease.
Materials and Methods: Hospital based case control study was conducted on 50 cases each of COPD with and without PH in Sardar Patel Medical College, Bikaner, Rajasthan. Complete blood count and 2D-echocardiography were done, RDW-CV value and pulmonary artery systolic pressure (PASP) were observed.
Conclusion: As the mean RDW-CV values were significantly higher in subjects of COPD with PH than those of COPD without PH in all age groups and both sexes, so we conclude that RDW-CV value can be used as marker to predict PH in patients with COPD in absence of other co-morbidities. Moreover, RDW-CV value also correlates with severity of PH. However, this is a small study and further studies are required on this subject.

Keywords: COPD, inflammation, RDW-CV

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a common, preventable and treatable disease, that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to gases

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or noxious particles [1]. COPD is usually caused by exposure to noxious particles or gases and characterized by persistent airflow limitation and respiratory symptoms [1]. The Global Burden of Disease Study 2017 using data from multiple sources, estimated the point prevalence of COPD at 3.92% worldwide in 2017 (95% CI 3.52%-4.32%). The estimated COPD-attributable death rate was 42/100,000 (4.72% of all-cause deaths) and the estimated DALYs rate was 1068.02/100,000 [2]. COPD is currently the third leading cause of death worldwide, causing 6% i.e.3.23 million deaths in 2019 [3]. Pulmonary hypertension (PH) is one of the major complications of COPD and considered an independent prognostic factor for patients with COPD [4]. The lung disease most frequently associated with PH is COPD (PH-COPD), which is by far the most common cause of cor pulmonale, accounting for more than 80% of all cases [5]. However, the estimated prevalence of PH in patients with known COPD varies dramatically-from 2.7% +to 90.8% depending on the definition of PH and the study population [6]. European Respiratory Society guidelines 2019 in accordance with 6th World Symposium on Pulmonary Hypertension defines pulmonary hypertension as mPAP >20 mmHg [7]. The gold standard for this measurement is the right heart catheterization. A more convenient but less accurate measurement is by echocardiography which requires a tricuspid regurgitant jet to measure the pressure gradient across the valve and thus estimate pulmonary artery systolic pressure (PASP). Fayngersh V assessed the prevalence of PH in outpatient population with stable COPD using echocardiography, they classified PASP greater than or equal to 35 mm Hg as PH [8]. 6-minute walk distance (6MWD) is on average 28 m less in patients with PH compared to those with normal hemodynamics; in addition, PPA is an independent predictor of a low 6MWD in a multivariate model [9]. Exertional dyspnea is significantly worse and survival is significantly shorter compared to patients without severe PH.6 Adjusted 5-year survival rate is 62% for patients with an initial PPA of 25 mm Hg or less, whereas only 36% in patients who have an initial PPA higher than 25 mm Hg [10]. Even mild PH may have a significant negative impact on exercise tolerance and survival and that the presence of PH may be a more important prognostic factor than the severity of lung disease [11]. In patients with COPD the presence of PH is clinically important because it is associated with worse exercise tolerance and survival compared to COPD patients without PH. As echocardiography is a sophisticated tool and available at super speciality centers only we need a simple tool for screening of PH, which shall be readily available. RDW is routinely available in CBC reports fairly done at most centers. Red cell distribution width is measurement of coefficient of variation of red cell volume. Over the past decade, RDW has been associated with incipient myocardial infarction and heart failure in the general population has emerged as the one of the strongest predictor of poor survival in patients with established heart failure and coronary artery disease [12]. RDW has also been proposed as marker of immune activation correlating with levels of tumour necrosis factor alpha and interleukin-6. The process of inflammation and dysregulated hematopoiesis may be linked, since interleukin 6 is important for production of hepcidin in liver and thus may indirectly regulate iron metabolism [13, 14]. Thus increased level of immune activation as seen is patients with raised RDW may be the common link between raised RDW and pulmonary hypertension associated with COPD. However, the prediction value of RDW in pulmonary hypertension secondary to COPD patients is unclear. Hence, we evaluate their association in this study. According to Chemla [15] formula mPAP = 0.61(PASP) + 2 mmHg, so for mPAP of 20 mmHg we obtain PASP of 29.5 mmHg, therefore in this study we will consider pulmonary hypertension as pulmonary artery systolic pressure ≥ 30 mmHg above right atrial pressure.

Aims and Objectives

- To observe Red Blood Cell Distribution Width in Patients with chronic obstructive pulmonary disease.

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- To correlate Red Blood Cell Distribution Width value with pulmonary artery pressure as measured above right atrial pressure by 2D echocardiography in patients with chronic obstructive pulmonary disease.

Material and Method

- Hospital based case control study was conducted on 50 cases each of COPD with and without PH.
- Complete blood count and 2D-echocardiography were done, RDW-CV value and pulmonary artery systolic pressure (PASP) were observed.
- Mean and standard deviation were calculated for both groups, COPD with PH and COPD without PH.
- Unpaired 't' test was applied to determine significance.

Inclusion criteria

- Those who gave informed consent.
- Patients of age 40 years or older.
- Diagnosed cases of COPD.

Exclusion criteria

- Patients with history of respiratory disorder other than COPD.
- Patients with haemogram <10 g/dl and any hematological disease.
- Patients with diagnosed auto-immune or oncological disease.
- Patients with diagnosed hepatic disease or renal disease.
- Patients with diagnosed cardiac disease other than pulmonary hypertension or cor pulmonale.
- Patients with history of old or active pulmonary tuberculosis.
- Patients with diabetes mellitus or hypertension.

Results

- The p-values correlating RDW in these two groups in every age groups were found to be statistically significant.
- The p-value correlating RDW were found statistically significant in both sexes (male; p, 0.004 and female; p, 0.001.
- Mean PASP were found rising with rise in RDW. The p-value correlating these groups was found to be statistically significant 0.002
- The mean RDW was 18.65 ± 1.62 in COPD with PH group and 15.49±1.31 in COPD without PH group. Unpaired 't' test was applied, the p-value correlating these two groups was found to be statistically significant (p<0.001).
- The cutoff RDW CV value was calculated to be 17.6 and it was 61.36% sensitive and had a negative predictive value of 76%.

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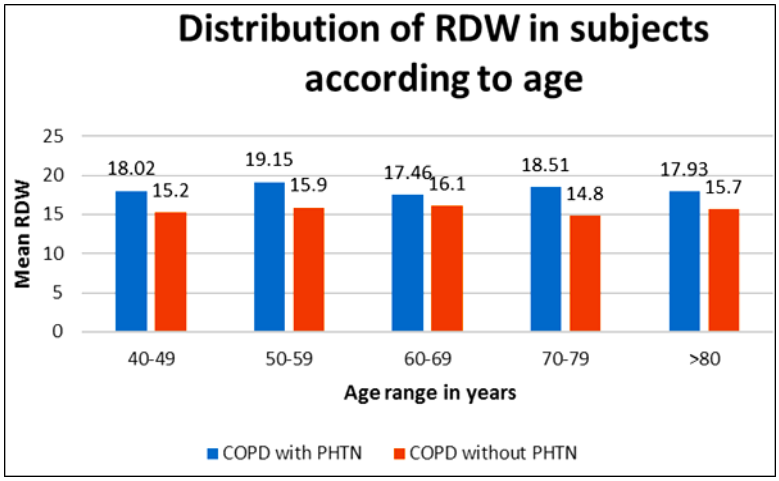
Distribution of RDW in subjects according to age

S. No	Age	COPD with PH	COPD without PH	p value
1	40-49	18.02±1.62	15.2 ± 1.47	0.001
2	50-59	19.15±1.36	15.9 ± 1.16	0.001
3	60-69	17.46±0.68	16.1 ±1.01	0.001
4	70-79	18.51±2.04	14.8 ± 1.20	0.001
5	>80	17.93±1.06	15.7 ± 1.7	0.05

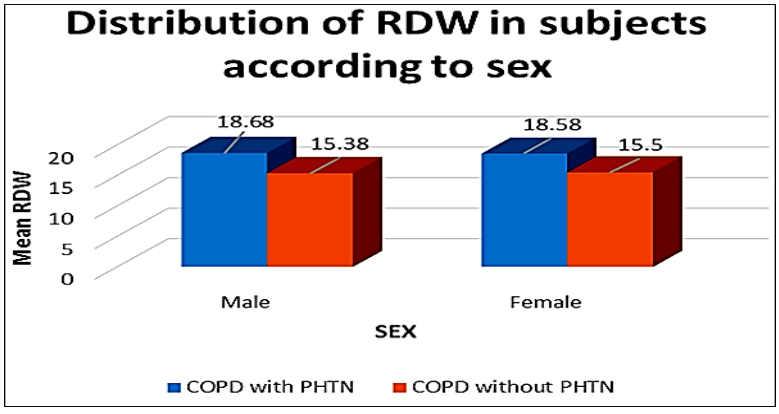
The p-values correlating these two groups in every age groups were found to be statistically signification.



Distribution of RDW in subjects according to sex

S. No	Sex	COPD with PH	COPD without PH	P value
1	Male	18.68±1.36	15.38±1.28	0.004
2	Female	18.58±1.41	15.50±1.10	0.001

The p-values were found statistically signification in both sexes (male 0.004 and female 0.001).



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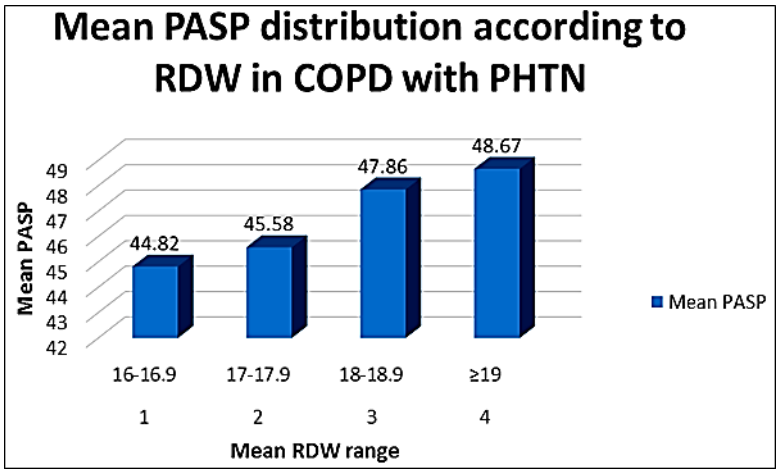
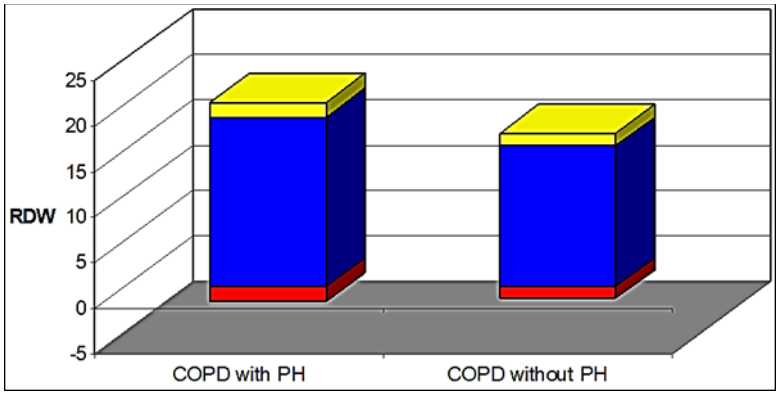
Mean PASP distribution according to RDW in COPD with PH		
S. No	RDW	Mean PASP
1.	<16	0
2.	16-16.9	44.82±10.31
3.	17-17.9	45.58±9.04
4.	18-18.9	47.86±9.90
5.	≥19	48.67±12.77
		p value = 0.0019

Mean PASP were found rising with rise RDW. The p-value correlating these groups was found to be statistically significant 0.002.



Mean distribution of RDW in study subjects

S. No.		COPD with PH	COPD without PH	P value
1	RDW	18.65±1.62	15.49±1.31	<0.001



Discussion

The prevalence of PH in COPD in various studies were variable, Higham *et al.* [16] found 57%, Gupta *et al.* [17] found 42.5%, D Radhakrishan *et al.* [19] found 40% and Alexander *et al.* [18] found 44%.

In our study, majority of patients (52.94%) were found in the age group of 60-69 years in both groups. The mean age was 62.7 ± 12.4 years and 56.05 ± 5.61 years in COPD with and without PH group respectively. The overall mean age of the subjects was (56.65 ± 9.35)

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years. A similar observation was made by Burrows *et al*. 108, who reported a mean age of 56.5 ± 7.4 years. In a study by Gupta *et al*. [20], the mean age was 55.4 ± 5.7 years. Dave L *et al*. [21] showed the mean age of 57.76 ± 7.90 years.

This study included 100 subjects with COPD of which 80% were males and 20% were females Exacerbations are commonly encountered by COPD patients. Cardiovascular comorbidities, especially PH and heart failure causes frequent exacerbations [22]. They tend to decrease the FEV1 further, increase the morbidity and mortality and adversely affect the quality of life.

The level of PH has a prognostic value in COPD. This has been demonstrated by several studies. In one of the study [23], the 5-year survival rates were 50% in mild PH, 30% in those with moderate to severe PH and 8% in very severe PH. Thus, a high degree of PH bears poor prognosis. In our study, the p values correlating mean RDW of COPD with and without PH groups were found statistically significant in all age groups and both sexes. Mean PASP were found rising with rise in RDW. The p-value correlating these groups was found to be statistically significant 0.002.

The mean RDW was 18.65 ± 1.62 in COPD with PH group and 15.49±1.31 in COPD without PH group. Unpaired 't' test was applied, the p-value correlating these two groups was found to be statistically significant (p<0.001).

The cutoff RDW CV value was calculated to be 17.6 and it was 61.36% sensitive and had a negative predictive value of 76%.

Seyhan EC [24] *et al*. also observed that COPD patients with high RDW were more likely to have PH than those without (61% vs 40%, p,0.02). The mean RDW was found rising with rise in PASP and mean PASP were found rising with rise in RDW. The p-value correlating these groups was found to be statistically significant; p, 0.001. Seyhan EC [25] *et al*. observed that RDW was positively correlated with right ventricular dysfunction (RVD) (p<0.001, r = 0.25) and pulmonary hypertension (PH) (p = 0.03, r = 0.14). T.E. Thayer [26] *et al*. observed strongest associations of RDW with pulmonary arterial hypertension (odds ratio [OR], 2.1; 95% confidence interval [CI], 1.9-2.3), P, 0.001. The mean pulmonary arterial pressure was associated with RDW and remained strongly significant even when controlling for mean pulmonary capillary wedge pressure. Increasing RDW was most strongly associated with right ventricular systolic pressure (RVSP) and right atrial pressure (P, 0.001, 1 3 10210). RDW was higher in the setting of right ventricular failure than left ventricular failure (P, 0.001). Laura A [27] *et al*., Patients with PH had significantly higher RDW values compared to patients without PH (16.0 ± 2.2 vs 14.4 ± 1.9%, respectively; p = 0.03). The study concluded that RDW is significantly higher in PH patients, without regard to disease etiology, when compared to age- and sex-matched non-diseased controls. Importantly, RDW is also higher in PH patients compared to at-risk patients. The ease of obtaining RDW as a biomarker may help detect incident PH at earlier stages among patients who are at high risk for development of PH. Jie Yang [28] *et al*. found that increased RDW level was observed in COPD-patients with PH compared with COPD patients without PH, with 15.10 ± 1.72% versus 13.70 ± 1.03%, respectively (p<0.001). RDW shared positive relationships with pulmonary artery (PA) systolic pressure (p, 0.014; r 0.390), and PA-to-ascending aorta (A) ratio (PA: A) (p, 0.001; r, 0.502). Multivariate analysis indicated that RDW and PA: A > 1 were the independent risk factors of PH secondary to COPD (p<0.05). The AUC of the RDW in patients with PH was 0.749 ± 0.054 (p<0.001). The optimal cut off value of RDW for predicti ng PH was 14 [29], with sensitivity and a specificity value of 69.2% and [30]. 8%, respectively. This study concluded that RDW is significantly increased in COPD patients with PH and thus may be a useful biomarker for PH secondary to COPD. The cutoff RDW CV value was calculated to be 17.6 and it was [31]. 36% sensitive and had a negative predictive value of 76%. Liu J127 *et al*. conducted meta-analysis, the results suggested that increased RDW can predict worse prognosis in PH (hazard ratio (HR)=1.27, 95% confidence interval (CI) 1.11-1.45). In addition, RDW showed prognostic value in retrospective studies (HR=1.32, 95% CI 1.15-1.51). Additionally, RDW may serve as a predictive biomarker of PH in Europe (HR= 1.33, 95% CI 1.18-1.49. Bai Y [30] *et al*. concluded that both MPV and RDW were

significantly elevated and correlated with disease severity in COPD patients with pulmonary heart disease and RDW can be biomarkers of pulmonary heart disease occurring secondary to COPD. Sincer [31] *et al*. also concluded that Red cell distribution width may be used to identify COPD patients with RV failure. Imran [32] *et al*. also concluded that there might be a relationship between the increased level of RDW and RV diastolic dysfunction in COPD patients.

Conclusion

As the mean RDW-CV values were significantly higher in subjects of COPD with PH than those of COPD without PH in all age groups and both sexes, so we conclude that RDW-CV value can be used as marker to predict PH in patients with COPD in absence of other co-morbidities. Moreover, RDW-CV value also correlates with severity of PH. However, this is a small study and further studies are required on this subject.

References

1. Global Initiative for Chronic Obstructive Lung Disease (GOLD): Global Strategy for the Diagnosis, Management and prevention of Chronic Obstructive Pulmonary Disease. (2022 REPORT). Available from: http://www.goldcopd.org.
2. GBD Chronic Respiratory Disease Collaborators. Prevalence and attributable health burden of chronic respiratory diseases, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Respir Med. 2020;8(6):585-96.
3. WHO fact sheet on the 10 leading causes of death in 2019. http://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-ofdeath
4. Mohan A, Premanand R, Reddy LN, Rao MH, Sharma SK, Kamity R, *et al*. Clinical presentation and predictors of outcome in patients with severe acute exacerbation of chronic obstructive pulmonary disease requiring admission to intensive care unit. BMC Pulm Med. 2006 Dec;6:27. Doi: 10.1186/1471-2466-6-27. PMID: 17177991; PMCID: PMC1764756.
5. Vance JW. Management of patients with cor pulmonale–acute and chronic. Prog Cardiovasc Dis. 1967;9(5):470-487.
6. Chaouat A, Bugnet AS, Kadaoui N, *et al*.: Severe pulmonary hypertension and chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2005;172(2):189-194.
7. Simonneau G, Montani D, Celermajer DS, *et al*. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J. 2019;53:180-1913. https://doi.org/10.1183/ 13993003. 01913-2018
8. Fayngersh V, Drakopanagiotakis F, Dennis McCool F, Klinger JR. Pulmonary hypertension in a stable community-based COPD population. Lung. 2011;189(5):377-382.
9. Cuttica MJ, Kalhan R, Shlobin OA, *et al*.: Categorization and impact of pulmonary hypertension in patients with advanced COPD. Respir Med. 2010;104(12):1877-1882.
10. Oswald-Mammosser M, Weitzenblum E, Quoix E, *et al*.: Prognostic factors in COPD patients receiving long-term oxygen therapy. Importance of pulmonary artery pressure. Chest. 1995;107(5):1193-1198.
11. Hurdman J, Condliffe R, Elliot CA, *et al*.: Pulmonary hypertension in COPD: results from the ASPIRE registry. Eur Respir J. 2013;41(6):1292-1301.
12. Allen LA, Felker GM, Mehra MR, Chiong JR, Dunlap SH, Ghali JK, *et al*. Validation and potential mechanisms of red cell distribution width as a prognostic marker in heart failure. J Card Fail. 2010;16(3):230-238.
13. Lippi G, Targher G, Montagnana M, Salvagno GL, Zoppini G, Guidi GC. Relation between red blood cell distribution width and inflammatory biomarkers in a large cohort of unselected outpatients. Arch Pathol Lab Med. 2009;133(4):628-632.
14. Perlstein TS, Weuve J, Pfeffer MA, Beckman JA. Red blood cell distribution width and

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mortality risk in a community-based prospective cohort Arch Intern Med. 2009;169:588-594.
15. Chemla D, Castelain V, Humbert M, *et al*., New formula for predicting mean pulmonary artery pressure using systolic pulmonary artery pressure*, Chest. 2004;126(4):1313-1317.
16. Kohansal R, Martinez-Camblor P, Agustí A, Buist AS, Mannino DM, Soriano JB. The natural history of chronic airflow obstruction revisited: an analysis of the Framingham offspring cohort. Am J Respir Crit. Care Med. 2009;180(1):3-10.
17. Martinez FJ, Han MK, Allinson JP, *et al*. At the Root: Defining and Halting Progression of Early Chronic Obstructive Pulmonary Disease. Am J Respir Crit. Care Med. 2018;197(12):1540-51.
18. Çolak Y, Afzal S, Nordestgaard BG, Lange P, Vestbo J. Importance of Early COPD in Young Adults for Development of Clinical COPD: Findings from the Copenhagen General Population Study. Am J Respir Crit. Care Med. 2021;203(10):1245-56.
19. Han MK, Agusti A, Celli BR, *et al*. From GOLD 0 to Pre-COPD. Am J Respir Crit. Care Med. 2021;203(4):414-23.
20. Hurst JR, Vestbo J, Anzueto A, *et al*. Susceptibility to exacerbation in chronic obstructive pulmonary disease. N Engl. J Med. 2010;363:1128-38.
21. De Torres JP, Ciro Casanova, Concepcion Hernandez, Juan Abreu, Angela Montejo de Garcini, *et al*. Gender associated differences indeterminants of quality of life in patients with COPD: a case series study. Health and Quality of Life Outcomes. 2006;4:72.
22. Wang Q, Takashima S, Wang JC, *et al*. Prevalence of emphysema in individuals who underwent screening CT for lung cancer in Nagano prefecture of Japan. Respiration. 2001;68:352-356.
23. Ray D, Abel R, Selvaraj K. A5yr prospective epidemiological study of chronic obstructive pulmonary disease in rural south India. Indian J Med Res. 2012;101:238-244.
24. Salvi S, Juvekar S, Londhe J. Prevalence of COPD in a rural population in India. Eur Respir J, 2011, 29-44.
25. Forey B, Thornton A, Lee P. Systematic review with meta-analysis of the epidemiological evidence relating smoking to COPD, chronic bronchitis and emphysema. BMC Pulmonary Medicine. 2011;11(1):36.
26. Jindal K, Aggraval A, Choudhary S. Asthma Epidemiology Study Group. A multicentric study on epidemiology of chronic obstructive pulmonary disease and its relationship with tobacco smoking and environmental tobacco smoke exposure. Indian J Chest Dis Allied Sci. 2006;48(23):9-27.
27. Singh S, Soumya M, Saini A. Breath carbon monoxide levels in different forms of smoking. Indian J Chest Dis Allied Sci., 2011, 53(25).
28. Smith CA, Harrison DJ. Association between poly-morphism in gene for microsomal epoxide hydrolase and susceptibility to emphysema. Lancet. 1997;350(9078):630-3.
29. Salvi S, Barnes P, *et al*. Chronic obstructive pulmonary disease in nonsmokers. The Lancet. 2009;374(9691):733-743.
30. World health statistics (internet), 2008. Available from http://www.who.int/whosis/whostat50
31. Prasad R, *et al*. Biomass fuel exposure and respiratory diseases in India. Bio Sci Trends. 2012;6(5):219-228.
32. International institute of population sciences (IIPS) and Macro International. National Family Health Survey, Mumbai: IIPS, 2007, 2.